



# Placebo-controlled trial of agomelatine in the treatment of major depressive disorder

S.H. Kennedy<sup>a,\*</sup>, R. Emsley<sup>b</sup>

<sup>a</sup> University Health Network, 200 Elizabeth Street, EN8-222, Toronto, ON, M5G 2C4, Canada

<sup>b</sup> University of Stellenbosch, Cape Town, South Africa

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## KEYWORDS

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Remission;  
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**Abstract** The efficacy and safety of flexible dosing with the antidepressant agomelatine (25–50 mg/day) was evaluated in a 6-week, double-blind, randomized, placebo-controlled study involving 212 patients who met Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria for major depressive disorder—current major depressive episode. Patients receiving agomelatine (25 mg and 50 mg/day) had a significantly lower mean Hamilton Rating Scale for Depression (HAM-D) score at endpoint compared with those who received placebo ( $14.1 \pm 7.7$  vs.  $16.5 \pm 7.4$ ,  $p=0.026$ ). Agomelatine significantly improved the response rate (49.1%;  $p=0.03$ ), time to first response ( $p=0.032$ ), and Clinical Global Impression-Severity of Illness score ( $p=0.017$ ), compared with placebo. These results were confirmed in a subgroup of patients with greater symptom severity. Agomelatine 50 mg also appeared to be effective and well tolerated in patients who failed to show improvement after 2 weeks on a dose of 25 mg/day. These results support the prescription of agomelatine 25 mg as the usual therapeutic dose, and suggest that increasing the dose to 50 mg may be beneficial for some patients without reducing tolerability.

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## 1. Introduction

Major depressive disorder (MDD) is estimated to have a lifetime prevalence of 16.6%, and is associated with significant morbidity and mortality (Kessler, 2005; Parikh and Lam, 2001). Although antidepressants constitute first-line treatment in the acute and long-term management of MDD, the effect of treatment is often suboptimal; at least

30% of depressed patients fail to achieve a satisfactory response (usually defined as a 50% reduction in symptom scores from baseline) to the index antidepressant and fewer than 50% achieve remission (defined as the virtual elimination of symptoms) (Frank et al., 1991; Kennedy et al., 2001). This variability in treatment effectiveness may be influenced by patient heterogeneity involving genetic, metabolic, personality, environmental and age differences (Kirchheiner et al., 2003; Meyer et al., 1996; Joyce et al., 2003) as well as treatment variables including drug selection, dose and treatment duration.

The introduction of selective serotonin re-uptake inhibitors (SSRIs) and subsequently serotonin and noradrenaline

\* Corresponding author. Tel.: +1 416 340 3888; fax: +1 416 340 4198.

E-mail address: sidney.kennedy@uhn.on.ca (S.H. Kennedy).

re-uptake inhibitors (SNRIs) was associated with better tolerability compared with the tricyclic and monoamine oxidase inhibitor antidepressants. This increased tolerability has been associated with improved adherence to treatment (Montgomery and Kasper, 1995). Nevertheless, there is room for further improvement because SSRIs are still associated with a number of adverse events including gastrointestinal disturbances, weight gain, day-time sleepiness, sexual dysfunction and discontinuation effects (Rosenbaum et al., 1998; Masand and Gupta, 1999; Vanderkooy et al., 2002; Zajecka, 2000). Additionally, lower rates of response or remission with SSRIs compared with SNRIs—venlafaxine and milnacipran (Thase et al., 2001; Clerc, 2001; Smith et al., 2002)—and to the tricyclic antidepressants (TCAs) (DUAG, 1990; Anderson, 2000; Sonawalla and Fava, 2001) have been reported.

These therapeutic shortcomings, together with the inherent heterogeneity of MDD, emphasize the need for alternative and improved antidepressants that are effective, well tolerated and offer flexibility with regard to dose adjustments. In addition to proven antidepressant activity, key requirements of improved antidepressants include rapid onset of action, and enhanced safety and tolerability. An antidepressant that meets these demands could be expected to reduce the burden on patients and their families, shorten the length of illness, with consequent reduction in health care costs, and ultimately lead to a superior outcome.

Recent evidence from pre-clinical (Bourin et al., 2004; Vacher et al., 2002; Bertaina-Anglade et al., 2002; Papp et al., 2002) and clinical studies (Loo et al., 2002) suggests that agomelatine, a specific agonist of  $MT_1$  and  $MT_2$  melatonergic receptors and a selective antagonist of serotonin 5-HT<sub>2C</sub> receptors (Chilman-Blair et al., 2003), has antidepressant properties. In an extensive European dose-range study involving over 700 depressed patients who met DSM-IV criteria for Major Depressive Disorder or Bipolar II Disorder, agomelatine 25 mg daily was as effective as paroxetine 20 mg daily, and significantly more effective than placebo (Loo et al., 2002). Furthermore, agomelatine alleviated the symptoms of anxiety associated with depression and provided a rapid onset of symptom relief compared with placebo. Using a stringent criterion of 6 or less on the 17-item Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) to define remission, the rates for agomelatine 25 mg/day (30.4%) and paroxetine 20 mg/day (25.7%) were similar. Agomelatine, but not paroxetine, showed a significant advantage over placebo on the HAM-D score in a subgroup of severely affected patients.

In view of the currently available information, the purpose of this placebo-controlled flexible-dosing study was to confirm the efficacy and safety of agomelatine 25–50 mg/day in patients who met criteria for a current episode of MDD (MDE).

## 2. Experimental procedures

### 2.1. Study design

This randomized, double-blind, placebo-controlled, parallel-group, international multicentre study was carried out in 21 centres across Finland, Canada and South Africa between

October 2002 and May 2004. Eligible patients received either agomelatine (administered as 1 agomelatine 25 mg tablet + 1 placebo tablet) or matched placebo (administered as 2 placebo tablets). At the end of the second week of treatment, the dose of agomelatine was doubled to 50 mg daily (administered as two agomelatine 25 mg tablets) in patients who were not considered to have improved sufficiently, based on HAM-D-17 and Clinical Global Impression (CGI; Guy, 1976) scores. Patients and investigators remained blind to treatment allocation and dosage throughout the study period, because randomization and any dose adjustment at week 2 were determined centrally.

The protocol was approved by local ethics committees, and the study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to study participation.

### 2.2. Patients

A total of 212 outpatients (aged 18–65 years) were enrolled. They were required to fulfil DSM-IV criteria for Major Depressive Disorder (current MDE of moderate or severe intensity) (American Psychiatric Association, 1994), have a score of  $\geq 22$  on the HAM-D score (Hamilton, 1960), and in the opinion of the investigator require antidepressant treatment. Patients with seasonal patterns, psychotic features or post-partum onset were not eligible for inclusion. Patients with other types of depression or psychiatric conditions (including bipolar I and II or dysthymic disorders) and those who displayed marked suicidal intent or known suicidal tendencies were also excluded, as were patients undergoing electroconvulsive treatment, insight-oriented or structured psychotherapy during the 3 months prior to assessment or light therapy during the 2 weeks before assessment. Patients who were otherwise eligible but who had not derived clinical benefit from two adequate antidepressant trials for the current episode, or from a previous trial of agomelatine, were also excluded.

### 2.3. Assessment of efficacy

Symptom severity was assessed at 0, 2, 4, and 6 weeks using the HAM-D and the CGI-Severity and CGI-Improvement scores. The primary outcome measure was the HAM-D final score in the intention-to-treat (ITT) population, using the last observation carried forward (LOCF) method. Secondary outcome measures defined a priori were: response to treatment (defined as a  $\geq 50\%$  decrease from the baseline HAM-D score); time to first response; remission (defined as a HAM-D total score  $\leq 6$ ); and CGI scores for severity of illness (CGI-S) and global improvement (CGI-I).

### 2.4. Statistical analyses

Efficacy analyses were performed on the ITT population, which comprised all patients who had received at least one dose of study medication and had at least one post-baseline evaluation for the HAM-D total score during the 6-week period. A subgroup analysis was also carried out, as defined a priori, in a group of severely depressed patients: this 'severe' subpopulation was defined by the generally accept-

ed definition of a baseline HAM-D score of 25 or higher (Montgomery et al., 2003; Guelfi et al., 2001).

The significance of difference in efficacy between agomelatine and placebo-treated groups was analysed using a two-sided Student's *t* test for independent samples. The difference between the treatment groups (agomelatine 25–50 mg or placebo), adjusted for centre and baseline on last post-baseline value, was analysed by a two-way analysis of covariance. A chi-square test and a logistic regression model with group, centre, and baseline as explanatory factors were used to compare responder and remitter rates. Finally, a log-rank test (Kaplan–Meier estimation) was used to determine time to first response. The same analyses were carried out on the a priori defined 'severe' subpopulation, which comprised 72% of the full ITT patients.

All analyses were carried out on a LOCF basis, and the significance level for global statistical tests was set at 0.05 (bilateral situation) for the two ITT populations (full sample, 'severe' sample).

## 2.5. Safety and tolerability

The population for safety analysis (safety set) included all patients known to have taken at least one dose of study medication. Clinical safety measures included a physical examination, routine laboratory tests (assessed centrally) and an electrocardiogram. These were completed before treatment administration and following cessation of treatment. Adverse events were recorded at each visit, and reasons for withdrawal were documented.

## 3. Results

### 3.1. Patient disposition and characteristics

A total of 212 patients (mean age  $42.5 \pm 12.5$  years, 60.2% women) were randomized to treatment. Demographic characteristics and disease factors were comparable between the agomelatine and placebo groups and are pre-

**Table 1** Demographics, diagnosis and depression severity at inclusion (intention-to-treat population)

Characteristic	Agomelatine ( <i>n</i> =106)	Placebo ( <i>n</i> =105)
Age (years), mean $\pm$ S.D. [range]	$42.2 \pm 12.7$ [18–65]	$42.2 \pm 12.0$ [20–62]
Sex, female (%)	65.1	55.2
Total HAM-D score, mean $\pm$ S.D.	$26.5 \pm 2.8$	$26.7 \pm 3.0$
CGI-S, mean $\pm$ S.D.	$4.8 \pm 0.7$	$4.8 \pm 0.7$
DSM-IV		
MDE single	21 (19.8%)	28 (26.7%)
MDE recurrent	85 (80.2%)	77 (73.3%)
Number of MDE, mean $\pm$ S.D.	$2.7 \pm 1.5$	$2.5 \pm 1.7$
Current MDE duration before inclusion (months), median	5.0	5.0

CGI-S, Clinical Global Impression of Severity; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; HAM-D, Hamilton Rating Scale for Depression; MDE, episode of major depressive disorder; S.D., standard deviation.

sented in Table 1. Post-baseline data for one patient in the agomelatine group were not available, resulting in an ITT population of 211 patients (106 patients in the agomelatine and 105 in the placebo group; Fig. 1).

The dosage of agomelatine was increased from 25 to 50 mg/day in 36 patients (34%); while 38 patients (37%) in the placebo group were similarly identified as the 'increased placebo' control group.

A total of 19 patients discontinued treatment during the acute phase of the study; 7 patients (6.5%) in the agomelatine group, and 12 patients (11.4%) in the placebo group (Fig. 1). Drug discontinuation due to lack of efficacy was observed more frequently in the placebo group (7 patients) than in the agomelatine group (2 patients).

Overall, 100 patients in the agomelatine group and 93 patients in the placebo group completed this 6-week trial, resulting in an overall completion rate of 91% in the ITT population.

## 3.2. Efficacy in full ITT population

### 3.2.1. Primary outcomes

Patients treated with agomelatine (25 and 50 mg/day) had a significantly lower mean HAM-D total score at endpoint compared with patients receiving placebo ( $14.1 \pm 7.7$  vs.  $16.5 \pm 7.4$ ,  $p=0.026$ ; Table 2; Fig. 2). In patients who received a dose increase, significant improvements in the HAM-D score were observed at week 6 ( $p=0.045$ ) in the agomelatine 25–50 mg arm (from  $26.1 \pm 2.6$  at baseline to  $17.5 \pm 7.4$ ) compared with the 'increased placebo' arm (from  $26.7 \pm 2.8$  to  $20.4 \pm 6.0$ ; Fig. 3).

### 3.2.2. Secondary outcomes: response, time to first response, remission

At week 6, the percentage of responders (patients who showed a HAM-D decrease of  $\geq 50\%$ ) was significantly higher for the agomelatine group compared with placebo (49.1% vs. 34.3%, respectively;  $p=0.03$ ). The survival analysis of time to first response also showed a significant difference in favour of agomelatine compared with placebo ( $p=0.032$ ).

The proportion of patients who were in remission (HAM-D total score  $\leq 6$ ) by the end of the acute treatment period (week 6) was not statistically different between the two treatment groups; however, a numerical difference was observed, with 20.8% in the agomelatine group compared with 13.3% in the placebo group achieving remission at the end of treatment (LOCF,  $p=0.152$ ).

### 3.2.3. Secondary outcome: CGI analysis

The CGI severity and improvement scores are shown in Table 2. There was a significant improvement in CGI-S scores with agomelatine compared to placebo at week 6 ( $p=0.017$ ); while CGI-I scores were observed to favour treatment with agomelatine compared to placebo, they did not reach statistical significance.

## 3.3. Efficacy in 'severe' subpopulation

### 3.3.1. Primary outcome

In the 'severe' ITT subpopulation, treatment with agomelatine resulted in a significantly lower mean HAM-D total score at endpoint than with placebo ( $14.4 \pm 7.9$  vs.  $17.3 \pm 7.2$ ,

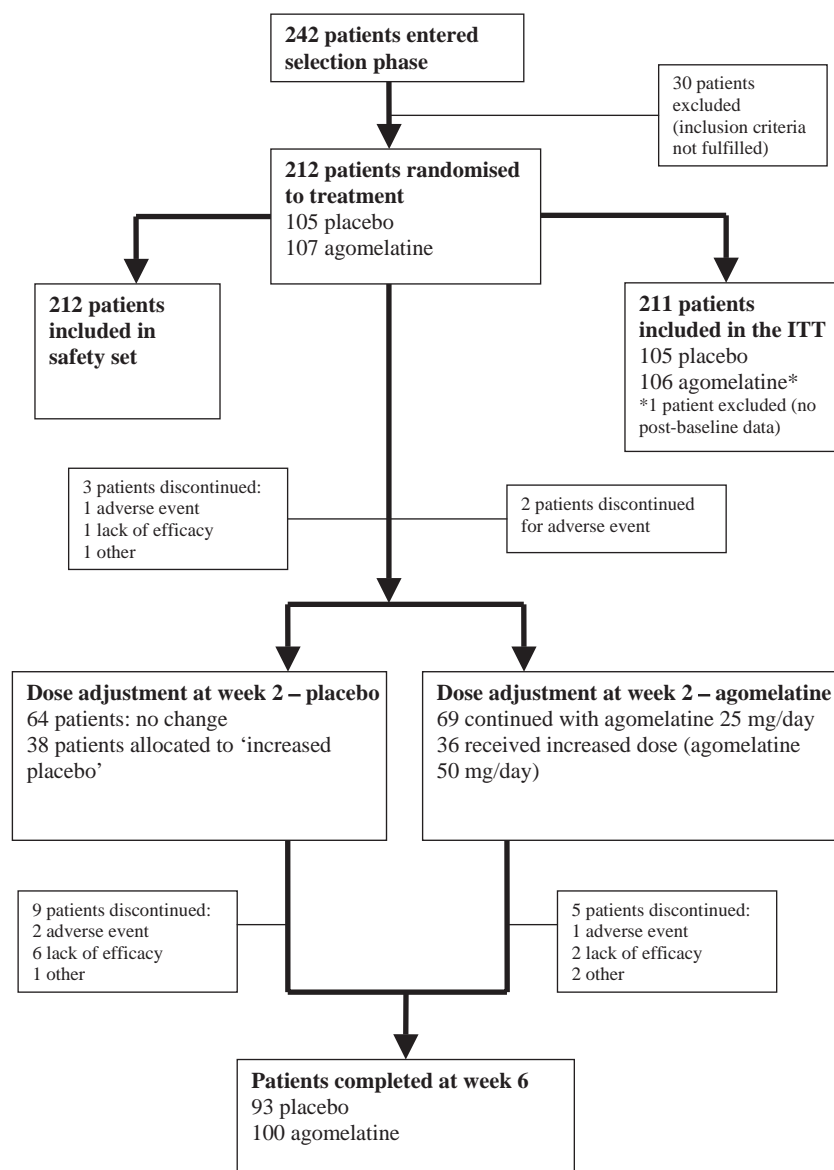


Figure 1 Patient disposition. ITT = intention to treat.

respectively,  $p=0.024$ ; Table 3). This difference in the mean HAM-D final score between agomelatine and placebo for the 'severe' subpopulation ( $2.72 \pm 1.19$ ; Table 3) exceeded the difference observed in the full ITT population ( $2.30 \pm 1.02$ ; Table 2).

### 3.3.2. Secondary outcomes: response, time to first response, remission

There was a significant difference in the percentage of responders following agomelatine vs. placebo in the 'severe' subpopulation (48.7% vs. 30.7% respectively,  $p \leq 0.024$ ). The survival analysis of time to first response also showed a statistically significant difference in favour of agomelatine compared with placebo ( $p=0.006$ ). As early as week 2, a difference of 1.45 was observed on the HAM-D total score between the two treatment groups, with a trend in favour of agomelatine ( $p=0.087$ ). Finally, a greater proportion of patients treated with agomelatine

achieved remission (21.1%) compared with the placebo group (12.0%;  $p=0.135$ ).

### 3.3.3. Secondary outcome: CGI analysis

Likewise, analysis of the CGI showed an advantage for agomelatine in the 'severe' ITT subpopulation. Patients treated with agomelatine had a significantly lower CGI-S score at week 6 compared to patients receiving placebo ( $3.2 \pm 1.4$  vs.  $3.7 \pm 1.3$  respectively,  $p=0.024$ ; Table 3), while a trend toward better global improvement with agomelatine compared to placebo was observed in the CGI-I score ( $2.4 \pm 1.1$  vs.  $2.7 \pm 1.0$ ,  $p=0.053$ ; Table 3).

### 3.4. Tolerability and safety

During the treatment period, 127 patients (61 in the agomelatine group and 66 in the placebo group) reported at least one treatment-emergent adverse event. These

**Table 2** Intention-to-treat (ITT) population: difference between agomelatine and placebo on Hamilton Rating Scale for Depression (HAM-D) total score, Clinical Global Impression (CGI) scores (CGI severity [CGI-S] and CGI global improvement [CGI-I])—last post-baseline value

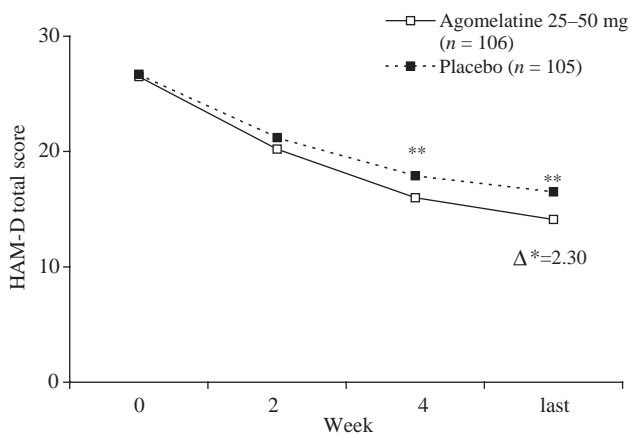
Scores	Agomelatine (n = 106)	Placebo (n = 105)
<b>HAM-D</b>		
Baseline score, mean ± S.D.	26.5 ± 2.8	26.7 ± 3.0
Final score, mean ± S.D.	14.1 ± 7.7	16.5 ± 7.4
Estimated between-group difference (S.E.)*	2.30 (1.02)	2.30 (1.02)
[95% C.I.]	[0.28; 4.31]	
p value	0.026	0.026
<b>CGI-S</b>		
Baseline CGI-S score, mean ± S.D.	4.8 ± 0.7	4.8 ± 0.7
Endpoint CGI-S score, mean ± S.D.	3.2 ± 1.3	3.6 ± 1.3
Estimated between-group difference (S.E.)	0.44 (0.18)	0.44 (0.18)
[95% C.I.]	[0.08; 0.80]	
p value**	0.017	0.017
<b>CGI-I</b>		
Endpoint CGI-I score, mean ± S.D.	2.4 ± 1.1	2.7 ± 1.1
Estimated between-group difference (S.E.)	0.25 (0.15)	0.25 (0.15)
[95% C.I.]	[-0.05; 0.56]	
p value**	0.098	0.098

C.I., confidence intervals; S.D., standard deviation; S.E., standard error.

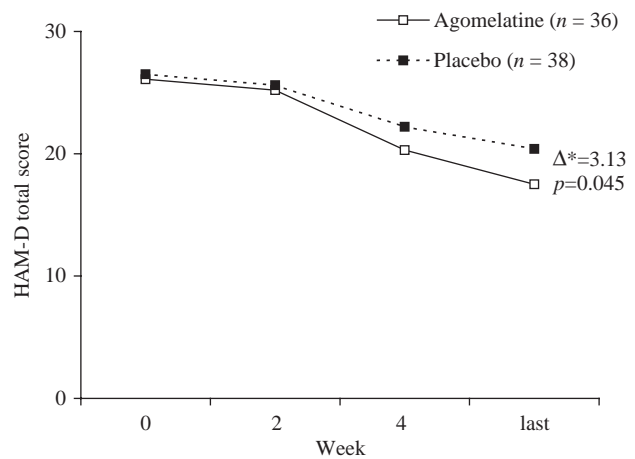
\* Adjusted on centre and baseline.

\*\* Mann–Whitney test.

events were considered to be related to treatment in 70 patients: 32 in the agomelatine group and 38 in the placebo group. Of the main adverse events, dizziness, nasopharyngitis and influenza were more common in the agomelatine



**Figure 2** HAM-D total scores over time in full ITT population. \*Adjusted on centre and baseline, last observation carried forward. \*\* $p < 0.05$ .



**Figure 3** HAM-D total score over time in patients who received a dose increase at 2 weeks. \*Adjusted on centre and baseline; last observation carried forward.

group than in the placebo group (9.3% vs. 4.8%, 6.5% vs. 3.8%, and 6.5% vs. 2.9%, respectively). In contrast, headache (20.0%), nausea (7.6%), fatigue (5.7%), dry mouth (4.8%),

**Table 3** ‘Severe’ subpopulation: difference between agomelatine and placebo on Hamilton Rating Scale for Depression (HAM-D) total score, Clinical Global Impression (CGI) scores (CGI severity [CGI-S] and CGI global improvement [CGI-I])—last post-baseline value

Scores	Agomelatine (n = 76)	Placebo (n = 75)
<b>HAM-D</b>		
Baseline score, mean ± S.D.	27.7 ± 2.3	28.1 ± 2.4
Final score, mean ± S.D.	14.4 ± 7.9	17.3 ± 7.2
Estimated between-group difference (S.E.)*	2.72 (1.19)	2.72 (1.19)
[95% C.I.]	[0.37; 5.08]	
p value	0.024	0.024
<b>CGI-S</b>		
Baseline CGI-S score, mean ± S.D.	5.0 ± 0.6	5.0 ± 0.6
Endpoint CGI-S score, mean ± S.D.	3.2 ± 1.4	3.7 ± 1.3
Estimated between-group difference (S.E.)	0.48 (0.22)	0.48 (0.22)
[95% C.I.]	[0.06; 0.91]	
p value**	0.024	0.024
<b>CGI-I</b>		
Endpoint CGI-I score, mean ± S.D.	2.4 ± 1.1	2.7 ± 1.0
Estimated between-group difference (S.E.)	0.30 (0.17)	0.30 (0.17)
[95% C.I.]	[-0.03; 0.63]	
p value**	0.053	0.053

C.I., confidence intervals; S.D., standard deviation; S.E., standard error.

\* Adjusted on centre and baseline.

\*\* Mann–Whitney test.

and diarrhoea (4.8%) were more common in the placebo group.

Treatment-related severe emergent adverse events were reported by 2 patients in the agomelatine group (1 case of dizziness and 1 of pruritis) and 6 patients in the placebo group: headache (2), insomnia (1), dry mouth (1), nausea (1), palpitations (1), chest tightness (1), decreased appetite (1), and nightmare (1). Inadequate control of diabetes mellitus, not related to study treatment, occurred in one patient in the agomelatine group.

#### 4. Discussion

Agomelatine, in a flexible-dose regimen of 25–50 mg, was significantly more effective than placebo in the treatment of MDD. This study confirms the efficacy of agomelatine 25–50 mg in both moderate and severe major depression, and shows the usefulness of a dose increase to 50 mg in patients who fail to show early improvement. The significantly higher rate of responders to agomelatine (49.1%) vs. placebo (34.3%) and the shorter time to first response further support the clinical efficacy of agomelatine.

These findings suggest that agomelatine is as effective as currently available antidepressants across classes—TCA, SSRI and dual action (e.g., venlafaxine and bupropion). The rate of responders to agomelatine (49%) in our study is comparable to a 46% responder rate in a TCA meta-analysis of 32 trials, with similar placebo responder rates in both trials—34% in this agomelatine trial compared with 31% in the TCA meta-analysis (Storosum et al., 2001). In a pooled analysis of eight randomized controlled trials (RCTs) comparing SSRIs with venlafaxine, however, the HAM-D-21 placebo responder rate was higher than in the present study at 42%, consequently, the responder rates for venlafaxine and SSRIs were also higher at 64% and 57%, respectively (Stahl et al., 2002). Nevertheless, if drug–placebo differences are taken into account, the agomelatine–placebo difference of approximately 15% is equivalent to the SSRI–placebo difference (also 15%), while the venlafaxine–placebo difference was approximately 22%. Likewise, in a pooled analysis of individual patient data from a complete set of studies (seven RCTs) comparing bupropion to various SSRIs, placebo rates were relatively high at 51%. In this pooled analysis, the drug–placebo difference in responder rates was 11% for bupropion and 12% for SSRIs (Thase et al., 2005).

From a clinical perspective, efficacy of antidepressants in severely depressed patients is very important because this patient group is often perceived as difficult to treat and less responsive to SSRI therapy (Clerc, 2001; Sonawalla and Fava, 2001; DUAG, 1990). The superior rate of responders to agomelatine in the ‘severe’ subpopulation of depressed patients in this study is therefore highly relevant. The response rate of 48.7% in this ‘severe’ subpopulation of depressed patients treated with agomelatine compares favourably to reports with other antidepressants (Llorca et al., 2005).

In line with a previous study, in which agomelatine was associated with early clinical improvement (Loo et al., 2002), this study also provides evidence of an early response in the ‘severe’ subpopulation. This observation is of particular importance because early improvement is not

only thought to lead to better compliance but is also seen to be a strong predictor of later stable response and remission (Szegedi et al., 2003).

Those patients who showed virtually no improvement after receiving agomelatine 25 mg for 2 weeks, achieved a significant benefit from a dose increase to 50 mg/day. At 6 weeks, 27.8% of this patient population were responders compared with only 13.2% in the placebo dose-adjustment control group. Since final response and remission rates are predicted by early improvements, and persistent non-response during the first weeks of treatment is often associated with later treatment failure (Nierenberg et al., 1995; Kennedy et al., 2001; Nierenberg, 2003), the finding of the improvement in depression scores following an increase of the dose of agomelatine at week 2 suggests that this treatment strategy is likely to be of clinical advantage in patients who respond poorly to treatment at an early stage, and emphasizes the importance of flexible dosing regimens.

The design of antidepressant clinical trials, particularly with regard to dosing schedule, has come under close scrutiny recently. A review of placebo-controlled fixed- and flexible-dose studies from the Food and Drug Administration Summary for Basis of Approval Reports indicated that flexible-dose studies generated results that were in favour of the active drug. This advantage is due, in part, to a significantly lower magnitude of symptom reduction with placebo in traditional flexible-dose trials compared with fixed-dose trials (Khan et al., 2003). One reason for this bias is likely to be the failure of adequate blinding to treatment allocation following the dose adjustment. A novel aspect of this study was that the criteria for dose adjustment were defined centrally and not disclosed to investigators or patients throughout the study. This limited the effects that an open change of dosage may exert on the evolution of depressive symptoms.

A particularly impressive aspect of this study was the high tolerability and low drop-out rates during treatment with agomelatine. The side-effect profile of agomelatine was similar to that of placebo. The frequency of adverse events (considered as treatment related by investigators) was marginally lower among patients receiving agomelatine (30.2%) than among patients receiving placebo (36.2%). Dizziness, nasopharyngitis and influenza were the most common emergent adverse events reported for agomelatine; however, no single adverse event was found to be statistically more common in the agomelatine group than in the placebo group. The rate of discontinuation due to adverse events was generally low, in accordance with previous reports (Loo et al., 2002), and almost identical between the placebo (2.9%) and agomelatine (2.8%) groups. Of the 211 patients who were included in the full sample, 193 completed the trial. This discontinuation rate (9%) compares very favourably to the discontinuation rate in a recently reported meta-analysis, where 34.5% in the active group and 35.1% in the placebo group discontinued treatment (Storosum et al., 2001). Although not the focus of this study, discontinuation-emergent symptoms are of considerable clinical concern and did not occur following agomelatine discontinuation (Montgomery et al., 2004).

In conclusion, the results of this study confirm the efficacy and safety of agomelatine 25 mg at the target dose, while also showing that an increase to agomelatine 50

mg can be clinically efficacious. Flexibility in the dosing regimen may be particularly beneficial for depressed patients who are slower to show initial improvement with treatment. These findings suggest that agomelatine possesses a number of attributes that are important in the treatment of depression: significant efficacy in depressed patients across a spectrum of severity, early onset of action, an excellent safety and tolerability profile (as reflected in the low number of adverse events), a low discontinuation rate and dosage flexibility.

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